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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ADENO-ASSOCIATEDVIRAL VECTORS AND METHODS FOR THEIR PRODUTION FROM HYBRID ADENOVIRUS AND FOR THEIR USE

(57) Abstract: A recombinant hybrid virus, including: (a) a deleted adenovirus vector genome comprising the adenovirus 5' and 3' *cis*-elements for viral replication and encapsidation, and further comprising a deletion in an adenovirus genomic region selected from the group consisting of: (i) the polymerase region, wherein said deletion essentially prevents the expression of a functional polymerase protein from said deleted region and said hybrid virus does not otherwise express a functional polymerase protein, (ii) the preterminal protein region, wherein said deletion essentially prevents the expression of a functional preterminal protein from said deleted region, and said hybrid virus does not otherwise express a functional preterminal protein, and (iii) both the regions of (i) and (ii); and (b) a recombinant adeno-associated virus (AAV) vector genome flanked by the adenovirus vector genome sequences of (a), said recombinant AAV vector genome comprising (i) AAV 5' and 3' inverted terminal repeats, (ii) an AAV packaging sequence, and (iii) a heterologous nucleic acid sequence, wherein said heterologous nucleic acid sequence is flanked by the 5' and the 3' AAV inverted terminal repeats of (i). Methods of making and using the recombinant hybrid virus are also disclosed.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/13323

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12N 15/85, 15/861, 15/864, 15/52
US CL : 435/320.1; 424/93.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/320.1; 424/93.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 6,251,677 B1 (WILSON et al.) 26 June 2001 (26.06.2001), see entire reference, especially col. 4-12, 41-44.	1-4, 10-22, 25-27, 35, 50-54 --- 23, 24, 28-34, 55
X — Y	WO 00/11149 A1 (UAB RESEARCH FOUNDATION) 02 March 2000 (02.03.2000), pages 36-39, 42-44, Fig. 10C, Fig. 15B.	1-3, 5-7, 9-13, 15, 16, 19-22, 25-27, 35 --- 28-34
X	LIEBER et al. Integrating adenovirus-adeno-associated virus hybrid vectors devoid of all viral genes. Journal of Virology. November 1999, Vol. 73, No. 11, pages 9314-9324, especially Abstract, page 9314; page 9315-9318.	1-4, 12-22, 26, 27, 35
Y	US 5,962,313 A (PODSAKOFF et al.) 05 October 1999 (05.10.1999), co. 11-12, 27-29.	28-33
Y	PAULY et al. Intercellular transfer of the virally derived precursor form of acid alpha-glucosidase corrects the enzyme deficiency in inherited cardioskeletal myopathy Pompe disease. Human Gene Therapy. 20 March 2001, Vol. 12, pages 527-538, see entire reference.	23-33

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DING et al. Long-term efficacy after [E1-, polymerase-] adenovirus-mediated transfer of human acid-alpha-glucosidase gene into glycogen storage disease type II knockout mice. Human Gene Therapy. 20 May 2001, Vol. 12, pages 955-965, see entire reference.	23-33
P, X	SUN et al. Long-term correction of glycogen storage disease type II with a hybrid Ad-AAV vector. Molecular Therapy. February 2003, Vol. 7, No. 2, pages 193-201, especially page 200.	1-4, 10, 12-15, 19-22, 26-33, 35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/13323

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claim Nos.: 36-49, 56-67
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-35, 50-55

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Continuation of Item 4 of the first sheet:
The title does not accurately summarize the invention. The new title is:

ADENO-ASSOCIATED VIRAL VECTORS AND METHODS FOR THEIR PRODUCTION FROM HYBRID ADENOVIRUS AND FOR THEIR USE

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-67, drawn to a hybrid adenovirus comprising an AAV vector genome, and method of use to transfect cells.

Group II, claim(s) 68-76, 109-122, 141, drawn to an AAV vector comprising GAA coding sequence, and method of use in treatment of subject .

Group III, claim(s) 77-108, 123-140, 142, drawn to a composition of AAV6 particles and method of using same for treatment of a subject.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I is directed to a class of adenovirus vector comprising an AAV vector genome, wherein the vector genome lacks sequence encoding either the polymerase or preterminal protein, i.e. it has a deletion of at least part of the adenoviral E2B region. The special technical feature is said to be the deletion of coding sequence for one of the E2B proteins. However, Wilson et al. US 6,251,677 discloses a hybrid adenoviral vector comprising an AAV vector genome and lacking coding sequence for both the E2B proteins (see claims 7 and 8). Thus, this technical feature is not special. Furthermore, the AAV vector of group II and AAV6 composition of group III are structurally different vectors from that of group I, and do not share the technical feature of group I.

Group II is directed to a generic AAV carrying a transgene encoding GAA. The special technical feature is said to be the inclusion of the GAA transgene in an AAV vector. However, Podsakoff et al., US 5,858,351 (e.g. see claim 25) and Podsakoff et al., US 5,962,313 (e.g. see claim 2) describe AAV vectors comprising a GAA transgene and their use in treatment. Thus, this technical feature is not special. Also, this technical feature is not required of either group I or III.

Group III is directed to a vector composition of AAV6 particles. The special technical feature is said to be the AAV6 capsid proteins in the particles. However, Russell et al. US 6,156,303 and McClelland et al., WO 02/063025 both describe AAV6 compositions and their use in treatment of subjects. Thus, this technical feature is not special. Also, this technical feature is not required of either group I or II.

Continuation of B. FIELDS SEARCHED Item 3:
MEDLINE, EMBASE, BIOSIS, CAPLUS, SCISEARCH, USPT, PGPB
search terms: aav, adeno-associated, adenovir?, hybrid, chimer?, e2b, polymerase, terminal or preterminal protein, Amalfitano, Koeberl, acid maltase, acid alpha glycosidase